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Chairman Barton, Congressman Dingell, and Ladies and Gentlemen:

Thank you for inviting me to testify before the Subcommittee on Health of the Committee on Energy and Commerce.

I am a rheumatologist by clinical training with research interests and expertise in drug safety and epidemiology. My group and I at Stanford University were instrumental in pointing out the risks of painkillers such as ibuprofen (Motrin) and Aleve (a class of drugs called NSAIDs). Our NIH sponsored research over the years has allowed us to identify patients who have a high risk of serious stomach bleeding from such drugs and potential ways to avoid such risks. I have been working in this research area of drug safety and outcomes research for almost 15 years, and have published extensively in the medical literature. I am currently working with large public datasets such as Medicare and Medicaid to study early safety signals of medications. I lecture medical students, residents and other physicians, both at Stanford, and in conferences worldwide, on many of these issues.

I have been asked to comment on the notion that FDA represents an effective, concerned and independent regulatory entity that can be relied upon to require and accurately analyze in a timely manner all information necessary to assess a drug or device's safety and efficacy profile and that it promptly informs the prescribing and the patient community through complete and accurate and understandable labeling. I will use the example of the approval and withdrawal of rofecoxib (Vioxx) as a case-study. It is not my intention to catalogue all the errors made, but rather to highlight the lessons that we have learnt and the knowledge that we can derive from this episode so that early signals are not missed again with another drug.

First of all, let me start by stating for the record my admiration for the FDA scientists and medical reviewers. They are some of the smartest individuals in the medical field, and have dedicated their lives to public service. They work long hours, in jobs that are mostly invisible to the public they try to protect, for salaries that are a fraction of what they could make outside the FDA. But they work within a system that is far from perfect – witness the Vioxx and anti-depressant episodes.

1. Pre-approval Clinical Trials are not designed for studying drug safety

In a clinical trial, patients are assigned randomly to receive the study drug or the comparison treatment, and they are followed for the health outcomes of interest. The clinical trial is the optimal method of assessing the efficacy of medications, but often not its safety. For example, clinical trials to study the efficacy of an arthritis pain medicine can be conducted in a few hundred patients who are followed for 6 weeks. But such a study is too small to evaluate the effects of a medication on health outcomes such as heart attack or stroke. Studies of thousands of patients followed for several years are often needed to provide confidence in the evaluation of these

outcomes. And therein lays a problem. The current system of drug approval at the FDA relies on clinical trials designed for efficacy – while these trials provide information to evaluate if the drug works, there are very often not sufficient to assess its safety.

Another problem is the fact that many clinical trials are performed in an "optimal" population, and exclude people who may be at risk for suffering the maximum harm from a drug – such as those with a weak heart or the elderly or pregnant women. So, there is little safety data collected in these high-risk populations.

In the current system of drug approval, trials designed to assess the safety of a drug are often performed after its approval – the so-called post-marketing studies. But these are rarely completed. A drug is considered "safe" unless proven otherwise. While this system brings rapid drug approvals, it does raise the rare possibility of sometimes causing serious harm from side-effects not discovered in clinical trials.

2. The system is designed for rapid drug approval, not a careful review of drug safety – the Vioxx example.

The first principle of medicine is *primum, non nocere* – first do no harm. It is extremely important that clinical trial data be carefully studied and if there is any indication – even a small one – that there is a possible risk of serious harm, the approval of the drug should be deferred till appropriate large-scale data is collected. How well equipped are we to do that today? Let me illustrate with the Vioxx example.

When Merck filed for the approval of Vioxx in the US, it submitted data on 58 studies (that included 3629 patients treated with Vioxx) to the FDA. However, only 371 and 381 patients had received doses of 12.5 mg or 25 mg for more than 1 year, and only 272 had received doses of 50 mg for at least 6 months. These studies were adequate to study the efficacy of Vioxx on pain relief, but did not have enough power to look at serious adverse vents such as heart attacks and strokes. Nevertheless, there were early signs of serious problems. In a careful FDA review of Merck's new drug application for Vioxx, Dr. Villalba (exhibit 10) noticed (and I quote) that "thomboembolic events [such as heart attack and stroke] are more frequent in patients receiving VIOXX than placebo…" [page 105]. Among 412 patients taking placebo, 1 had a cardiovascular event (0.24%). In contrast, among the 1631 patients receiving 12.5 mg or more of VIOXX daily, 12 had a cardiovascular event (0.74%) (6) – a three-fold increase in risk. Many scientists would consider this three-fold difference as an early warning sign. But at that time, there were no adequate data to make a firm conclusion one way or another. In fact, the FDA reviewer went on to point out that: "With the available data, it is impossible to answer with complete certainty whether the risk of cardiovascular and thromboembolic events is increased in patients on rofecoxib. A larger database will be needed to answer this and other safety comparison questions" [page 105].

What happens next? Does the FDA require Merck to conduct larger and more definitive studies? After all, the drug was no more effective than any other available pain-killer in the US – and there were nearly 30 such drugs available in the US. Further, another drug – the cox-2 inhibitor celebrex- which had no such signal for heart attacks had been already available in the US market 6 months prior. A combination of two older drugs – a pain-relieving drug such as motrin with a drug that protects the stomach such as prilosec – is as effective and almost as safe on the stomach as Vioxx, with no heart attack risk. There was certainly no emergent need to approve Vioxx without further studies if there were lingering safety concerns. The trade-off of heart attacks for the rare instances of stomach bleeds is not a reasonable one. Remember, primum non nocere – first, do no harm. Instead, the drug was approved by the FDA in a priority review within 6 months – with no discussion on the heart attack trade-off. The system that is designed to approve drugs rapidly works – at a cost that we all know now.

3. There is no mechanism for conditional or time-limited approval.

Once a drug is approved, the FDA has little power to force a drug company to do safety studies. Let us look at Vioxx. From the time the NDA was filed to the ultimate withdrawal of the drug, FDA medical reviewers repeated noted the increase in heart problems with the drug, in multiple studies. The signals were not definitive because there were no large safety studies. FDA reviewers repeatedly noted the need for such studies. On March 12, 2002, Dr. Villalba wrote to Dr. Goldkind (Deputy Division Director): "Adequately powered and prospectively designed studies are necessary to definitively address cardiovascular safety issues with Vioxx". Merck would not do any, and in fact, cancelled the one study that could have provided the answer in 2002. The New York Times recently reported that Merck decided a cardiovascular outcome study would send the "wrong" marketing and public relations signal. Why ask a question if you do not want to know the answer? Instead Merck proposed a pooled analysis of ongoing clinical trials for new indications. On December 19, 2002, the FDA sent a letter to Merck stating that this approach "..might not be sufficient to address the ongoing cardiovascular safety concerns surrounding Vioxx."

Four years before the withdrawal of Vioxx, the FDA had "ongoing cardiovascular safety concerns surrounding Vioxx". Concerns that had started before the drug was approved. Yet, the sponsor would not do definitive studies to address these safety concerns. So what happens – life goes on, millions of people take the drug, blissfully unaware of "ongoing cardiovascular safety concerns" of their regulatory agency. And the band plays on…

It is my recommendation that a system of conditional or time-limited approvals should be instituted. This way, if there are any emerging safety problems with a drug after its approval, the FDA can require companies to do large safety studies within a certain time period.

4. There is no good mechanism of informing the prescribing physicians or public of FDA's concerns.

In my opinion, this is the single most important problem of communication with the system. While the drug companies spent hundreds of millions of dollars in touting the benefits of their drugs in direct-to-consumer advertisements and sales calls to physicians, the FDA has no way to inform the public of its concerns, except through a process of label change.

Again, let us look at the Vioxx example. Multiple studies published by Merck in medical journals underplayed the risk of serious cardiovascular complications. The VIGOR trial was published in the New England Journal of Medicine, once of the most reputed medical journals in the world. However, the publication under-reported the true number of heart attacks in patients on Vioxx. (Four years later, Merck would say that those were preliminary numbers – but did the publication say that at that time?). While it prominently discussed the 50% reduction of stomach bleeds in patients taking Vioxx, it did not mention that in spite of this, patients on Vioxx had more serious adverse events, more hospitalizations and more deaths than patients on Naproxen. In addition, the true rates for cardiovascular thrombotic adverse events (a prespecified study endpoint in the protocol), hypertension and congestive heart failure, factors that may contribute to heart attacks and which were all higher in the Vioxx group - were not shown in the paper at all. The FDA knew the truth - but these concerns were never communicated to the prescribing physicians or public. In February 2001, the FDA put the correct numbers on its website – but how many physicians know how to navigate the FDA website? Why could the FDA not publish its own findings in the New England Journal?

In March 2000, Merck sent a letter to all its investigators to encourage the use of aspirin in patients on Vioxx who may be at risk for cardiovascular complications. For the next 4 years, Merck sales force would tell prescribing physicians that the use of aspirin would eliminate the increased heart attack risk seen with Vioxx. But studies that the FDA reviewed suggested that this was simply not true. For example, in a document released to public last week, Dr. Villalba's review of the ADVANTAGE study on November 28, 2001 states: "the use of low dose ASA for cardiovascular prophylaxis may not eliminate the excess of cardiovascular events on rofecoxib 25 mg compared to naproxen…" The FDA knew, but the prescribing physicians and the American public remained blissfully unaware – and the band played on…

Merck has repeatedly insisted that prior to the APPROVe study, there was no evidence of Vioxx's toxicity. In multiple scientific meetings and other communications with physicians, Merck presented data from Alzheimer's disease studies to claim that there was no heart attack risk from Vioxx. However, FDA memos released last week show that the FDA "never accepted the results from the Alzheimer's studies as a replacement for prospectively designed, placebo-controlled studies. Furthermore, the FDA repeatedly requested that these data be updated." Yet, it took more than a year from FDA's first request on December 9, 2002 to when it finally received the updated data on December 17, 2003. As early as 2001, the FDA already knew that in two Alzheimer's Disease studies, patients on Vioxx were almost twice as likely to die as those on placebo; updated safety data confirmed these findings. Yet, the FDA never released their analysis in any scientific meeting or any other communication to the public. Once again, the drug company continues to claim safety of its drug, the FDA knows otherwise, but the prescribing physicians and patients remain blissfully unaware. And the band plays on…

5. The label process is one of negotiations - let us make a deal…

There needs to be an open public discussion of the role of FDA in approving drugs and labels. The label is the practically the only way through which the FDA communicates with physicians. Last week, the FDA released a document titled "Sequence of Events with Vioxx, since opening of IND". I would encourage all of you to read it – and see for yourself how this process can be manipulated. Some quotes from this document:

> "The sponsor rejected FDA proposed labeling."
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> "The division requested that the sponsors reconsider their proposal…"
>
> "Merck cancelled the January 09, 2002 meeting."
>
> And many more.

The current process of labeling is one of negotiations - – if the "sponsor" does not agree with what the FDA wants, it can continue to stall or worse. In the meantime, it can continue to sell its drug and promote its cardiovascular safety in the scientific and lay media. And the band plays on.

Finally, one side gives in – the label is approved. A label that mostly supports Merck's position.

This process needs to be corrected, if need be, by new legislation. The FDA should be given the authority that is accorded to our judicial system – to make unilateral decisions on issues of public health safety, after appropriate public hearings, without having to negotiate and reach agreement with drug companies. The FDA should regulate the drug companies, not collaborate or negotiate with them if there is any question of public safety.

6. Absence of publicly-available information

The FDA approval process needs to be more open and subject to public scrutiny. Once a drug is approved, all the data supporting such approval should be put in the public domain. If this had been done with Vioxx, perhaps independent scientists would have been able to spot early signals. Similarly, all clinical study data submitted to the FDA should be available to the public after the drug is approved. Claims of "trade secrets" should not take precedence over public health and safety. Pharmaceutical companies should not be allowed to selectively disseminate only positive data.

The FDA should encourage its scientists to publish their findings – even if these findings challenge currently-held opinions. In fact, it is more important to hear views of dissent – only through an open discussion of all issues does science advance. Scientists like Dr. Graham and Dr. Mossholder should be encouraged to discuss their findings in public, and publish in the scientific literature.

7. Emphasis on Drug Safety

It is important for life-saving medications to be approved in a rapid fashion. However, there needs to be a renewed focus on drug safety as well. Current standards regard every drug as safe – even one that has multiple safety signals in clinical trials - unless it can be proven with 95% certainty that it is not. Such certainty requires large trials, which are not done – and the band plays on…If there is conditional approval, this will change.

An independent office of drug safety which does not report to the FDA new drug approval section should be established. Safety data on all new drug approvals must be vetted through this office. Such independent office should have the authority to conduct safety studies on approved drugs, or require that such studies be conducted if there are safety signals. Only then will be able to adhere to the principle of "Primum, Non Nocere" – First, Do No Harm.

Thank you.

Thank you.

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